REMARKS

The Examiner issued an advisory action dated June 17, 2005 in this application. The advisory action asserted that Applicants' amendments in the response to the final office action had raised new issues, necessitating additional consideration or search.

Applicant's counsel, upon receipt of the advisory action, conducted multiple telephone interviews with the Examiner. In the last interview, held July 7, 2005, the Examiner agreed that the amendments did not raise new issues. On the other hand, he uncovered a new reference, i.e., Cipollone et al. *Circulation*, 1997, 1109-1115 (Cipollone), and requested that Applicants comment on the relevance of this reference to the pending claims.

Applicants would like to discuss first the patentability of claims 1, 4, and 21, the independent claims, in view of Cipollone.

Claims 1 and 4 cover methods for assessing aspirin resistance and determining risk of a cardiovascular event, respectively. Each method includes comparing the concentration of a thromboxane A2 metabolite to a predetermined set containing four quartiles, which correspond to less than 15.1 ng/mmol creatinine, 15.1-21.8 ng/mmol creatinine, 21.9-33.7 ng/mmol creatinine, and greater than 33.8 ng/mmol creatinine, respectively. The patentability of these two claims resides at least in part in the unique thromboxane A2 metabolite concentration ranges of the four quartiles.

Cipollone teaches that when unstable angina patients are treated with aspirin, the urinary excretion of a thromboxane A2 metabolite is partly suppressed. It mentions that the samples from these patients have an average thromboxane A2 metabolite concentration of 102 pg/mg. Nowhere in Cipollone is disclosed or suggested the four unique concentration ranges required in claims 1 and 4. Thus, Cipollone does not anticipate or render obvious claims 1 and 4.

Claim 4 is also distinguishable from Cipollone on an additional ground. Claim 4 covers a method for determining risk of a cardiovascular event by comparing the concentration of a thromboxane A2 metabolite with a predetermined set containing four quartiles. Cipollone does not teach or suggest determining risk of a cardiovascular event based on a thromboxane A2 metabolite concentration. On one hand, it discloses that aspirin suppresses the urinary excretion

of a thromboxane A2 metabolite in unstable angina patients. On the other hand, it mentions "no patient in either group [treated with aspirin or treated with indobufen] developed myocardial infarction or sudden death during the study ..." See page 1111, left column, lines 61-63. In other words, Cipollone **teaches away** the correlation between suppressed concentrations of a thromboxane A2 metabolite in unstable angina patients treated with aspirin and the future occurrence of cardiovascular events such as myocardial infarction or sudden cardiovascular death. Thus, it clearly does not anticipate or render obvious claim 4, which covers a method based on such a correlation.

Applicants now turn to claim 21. This claim covers a method for determining relative risk of a cardiovascular event by determining whether the concentration of 11-dehydro thromboxane B2 in a urine sample exceeds 15.1 ng/mmol. According to this method, a 11-dehydro thromboxane B2 concentration greater than 15.1 ng/mmol is indicative of increased risk of a cardiovascular event.

As mentioned above, Cipollone does not teach a correlation between thromboxane A2 metabolite concentrations and the future occurrence of cardiovascular events. Thus, it does suggest determining relative risk of a cardiovascular event based on the concentration of 11-dehydro thromboxane B2, a thromboxane A2 metabolite, as required in claim 21. Moreover, Cipollone also does not disclose the specific concentration of 11-dehydro thromboxane B2 (15.1 ng/mmol) required in the method of claim 21 to determine the relative risk of a cardiovascular event. Thus, claim 21 is novel and unobvious over Cipollone.

Claims 5-9 and 16 depend from claim 4, claims 18 and 20 depend from claim 1, and claims 22-24 depend from claim 21. For the same reasons set forth above, these claims are also novel and unobvious over Cipollone.

To complete the record, Applicants would like to point out that as Cipollone is cited for the first time, the Examiner should have withdrawn the finality of the last issued office action and issued a new non-final office action. However, in the sole interest of expediting the prosecution of this application, Applicants have filed this supplemental response to the last office action to discuss the patentability of the pending claims in view of Cipollone and also paid a

three-month extension fee. **In all fairness, Applicants request that this application be reopened and the extension fee be refunded, should the Examiner still decide not to allow the application in view of the above remarks.**

CONCLUSION

Applicants submit that claims 1, 4-9, 16, 18, and 20-24, as pending, cover definite and enabled subject matter that is novel and unobvious over the prior art. Applicants request that all pending claims be allowed.

Enclosed is a $510 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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